International Journal of Child Care and Education Policy
2013, Vol. 7, No. 2, 15-31

Differential Susceptibility to Environmental Influences

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Evidence that adverse rearing environments exert negative effects particularly on children and adults presumed "vulnerable" for temperamental or genetic reasons may actually reflect something else: heightened susceptibility to the negative effects of risky environments and to the beneficial effects of supportive environments. Building on Belsky's (1997, 2005; Belsky & Pluess, 2009) evolutionary-inspired differential susceptibility hypothesis stipulating that some individuals, including children, are more affected—both for better and for worse—by their environmental exposures and developmental experiences, recent research consistent with this claim is reviewed. It reveals that in many cases, including both observational field studies and experimental intervention ones, putatively vulnerable children and adults are especially susceptible to both positive and negative environmental effects. In addition to reviewing relevant evidence, unknowns in the differential-susceptibility equation are highlighted.

Key words: early childhood education and care, preschool, policy, ethnic minority children, special needs children

Introduction

Most students of child development probably do not presume that all children are equally susceptible to rearing (or other environmental) effects; a long history of research on interactions between parenting and temperament, or *parenting-by-temperament interactions*, clearly suggests otherwise. Nevertheless, it remains the case that most work still focuses on effects of environmental exposures and developmental experiences that apply equally to all children—so-called main effects of parenti7ng or poverty or being reared by a depressed mother—thus failing to consider interaction effects, which reflect the fact that whether, how, and how much these contextual conditions influence the child may depend on the child's temperament or some other characteristic of individuality.

Research on parenting-by-temperament interactions is based on the premise that what proves effective for some

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individuals in fostering the development of some valued outcome—or preventing some problematic one—may simply not do so for others. Commonly tested are diathesis-stress hypotheses derived from multiple-risk/transactional frameworks in which individual characteristics that make children "vulnerable" to adverse experiences—placing them "at risk" of developing poorly—are mainly influential when there is at the same time some contributing risk from the environmental context (Zuckerman, 1999). Diathesis refers to the latent weakness or vulnerability that that a child or adult may carry (e.g., difficult temperament, particular gene), but which does not manifest itself, thereby undermining well-being, unless the individual is exposed to conditions of risk or stress.

After highlighting some research consistent with a diathesis-stress or dual-risk perspective, I raise questions—on the basis of other findings—about how the first set of data has been interpreted, advancing the evolutionary-inspired proposition that some children, for temperamental or genetic reasons, are actually more susceptible to *both* (a) the adverse effects of unsupportive parenting *and* (b) the beneficial effects of supportive rearing (Belsky, 1997, 2005; Belsky & Pluess, 2009, 2013a). Finally, I draw conclusions and highlight some "unknowns in the differential-susceptibility equation."

Diathesis-Stress, Dual-Risk and Vulnerability

The view that infants and toddlers manifesting high levels of negative emotion are at special risk of problematic development when they experience poor-quality rearing is widespread. Evidence consistent with this view can be found in the work of Morrell and Murray (2003), who showed that it was only highly distressed and irritable 4-month-old boys who experienced coercive and rejecting mothering at this age who continued to show evidence, 5 months later, of emotional and behavioural dysregulation. Relatedly, Belsky, Hsieh, and Crnic (1998) observed that infants who scored high in negative emotionality at 12 months of age and who experienced the least supportive mothering and fathering across their second and third years of life scored highest on externalizing problems at 36 months of age. And Deater-Deckard and Dodge (1997) reported that children rated highest on externalizing-behavior problems by teachers across the primary-school years were those who experienced the most harsh discipline prior to kindergarten entry and who were characterized by mothers at age 5 as being negatively reactive infants.

The adverse consequences of the co-occurrence of a child risk factor (i.e., a diathesis; e.g., negative emotionality)

and problematic parenting also is evident in Caspi and Moffitt's (2006) ground-breaking research on gene-by-environment (GXE) interaction. Young men followed from early childhood were most likely to manifest high levels of antisocial behavior when they had both (a) a history of child maltreatment and (b) a particular variant of the *MAO-A* gene, a gene previously linked to aggressive behaviour. Such results led Rutter (2006), like others, to speak of "vulnerable individuals," a concept that also applies to children putatively at risk for compromised development due to their behavioral attributes. But is "vulnerability" the best way to conceptualize the kind of person-X-environment interactions under consideration?

Beyond Diathesis-Stress, Dual-Risk and Vulnerability

Working from an evolutionary perspective, Belsky (1997, 2005; Belsky & Pluess, 2009) theorized that children, especially within a family, should vary in their susceptibility to both adverse and beneficial effects of rearing influence (see also Ellis, Boyce, Belsky, Bakermans- Kranenburg & van IJzendoorn, 2011). Because the future is uncertain, in ancestral times, just like today, parents could not know for certain (consciously or unconsciously) what rearing strategies would maximise reproductive fitness, that is, the dispersion of genes in future generations, the ultimate goal of Darwinian evolution. To protect against all children being steered, inadvertently, in a parental direction that proved disastrous at some later point in time, developmental processes were selected to vary children's susceptibility to rearing (and other environmental influences). In what follows, I review evidence consistent with this claim which highlights early negative emotionality and particular candidate genes as "plasticity factors" making individuals more susceptible to both supportive and unsupportive environments, that is, "for better and for worse" (Belsky, Bakerman-Kranenburg, & van IJzendoorn, 2007).

Negative Emotionality as Plasticity Factor

The first evidence which Belsky (1997, 2005; Belsky & Pluess, 2009) could point to consistent with his differential-susceptibility hypothesis concerned early negative emotionality. Children scoring high on this supposed "risk factor", particularly in the early years, appeared to benefit disproportionately from supportive rearing environments (Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg & van IJzendoorn, 2011). Feldman, Greenbaum, and Yirmiya (1999) found, for example, that 9-month-olds scoring high on negativity who experienced low levels of

synchrony in mother–infant interaction manifested more noncompliance during clean-up at age two than other children did. When such infants experienced mutually synchronous mother–infant interaction, however, they displayed greater self-control than did children manifesting much less negativity as infants. Subsequently, Kochanska, Aksan, and Joy (2007) observed that highly fearful 15-month-olds experiencing high levels of power-assertive paternal discipline were most likely to cheat in a game at 38 months, yet when cared for in a supportive manner such negatively emotional, fearful toddlers manifested the most rule-compatible conduct.

In the time since Belsky and Pluess (2009) reviewed evidence like that just cited, highlighting the role of negative emotionality as a "plasticity factor", even more evidence to this effect has emerged in the case of children. Consider in this regard work linking (1) maternal empathy (Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht, 2011) and anger (Poehlmann et al., 2012) with externalizing problems; (2) mutual responsiveness observed in the mother-child dyad with effortful control (Kim & Kochanska, 2012); (3) intrusive maternal behavior (Conway & Stifter, 2012) and poverty (Raver, Blair, & Willoughby, 2013) with executive functioning; and (4) sensitive parenting with social, emotional and cognitive-academic development (Roisman et al., 2012).

Experimental studies designed to test Belsky's (1997, 2005) differential-susceptibility hypothesis are even more suggestive than the longitudinal-correlational evidence just cited. Blair (2002) discovered that it was highly-negative infants who benefited most—in terms of both reduced levels of externalizing behavior problems and enhanced cognitive functioning—from a multi-faceted infant-toddler intervention program whose data he reanalyzed. Thereafter, Klein Velderman, Bakermans-Kranenburg, Juffer, and van IJzendoorn (2006) found that experimentally induced changes in maternal sensitivity exerted greater impact on the attachment security of highly negatively reactive infants than it did on other infants. In both experiments, environmental influences on "vulnerable" children were for better instead of for worse.

As it turns out, there is ever-growing experimental evidence that early negative emotionality is a plasticity factor. Consider findings showing that it is infants who score relatively low on irritability as newborns who fail to benefit from an otherwise security-promoting intervention (Cassidy, Woodhouse, Sherman, Stupica, & Lejuez, 2011) and infants who show few, if any, mild perinatal adversities—known to be related to limited negative emotionality—who fail to benefit from computer-based instruction otherwise found to promote preschoolers' phonemic awareness and early literacy (Van der

Kooy-Hofland, van der Kooy, Bus, van Ijzendoorn, & Bonsel, 2012). In other words, only the putatively "vulnerable"—those manifesting or likely to manifest high levels of negativity—experienced developmental enhancement as a function of the interventions cited. Similar results emerge among older children, as Scott and O'Connor's (2012) parenting intervention resulted in the most positive change in conduct among emotionally dysregulated children (i.e., loses temper, angry, touchy).

Genes as Plasticity Factors

Perhaps nowhere has the diathesis-stress framework informed person-X-environment interaction research more than in the study of GXE interaction. Recent studies involving measured genes and measured environments also document both for better and for worse environmental effects--in the case of susceptible individuals—as it turns out. Here I consider evidence pertaining to two specific candidate genes before turning attention to research examining multiple genes at the same time.

DRD4

One of the most widely studied genetic polymorphisms in research involving measured genes and measured environments pertains to a particular allele (or variant) of the dopamine receptor gene, *DRD4*. Because the dopaminergic system is engaged in attentional, motivational, and reward mechanisms and one variant of this polymorphism, the 7-repeat allele, has been linked to lower dopamine reception efficiency, van IJzendoorn and Bakermans-Kranenburg (2006) predicted this allele would moderate the association between maternal unresolved loss or trauma and infant attachment disorganization. Having the 7-repeat *DRD4* allele substantially increased risk for disorganization in children exposed to maternal unresolved loss/trauma, as expected, consistent with the diathesis-stress framework; yet when children with this supposed "vulnerability gene" were raised by mothers who had no unresolved loss, they displayed significantly less disorganization than agemates without the allele, regardless of mothers' unresolved-loss status (Bakermans-Kranenburg & van IJzendoorn, 2011).

Similar results emerged when the interplay between *DRD4* and observed parental insensitivity in predicting externalizing problems was studied in a group of 47 twins (Bakermans-Kranenburg & van IJzendoorn, 2007). Children carrying the 7-repeat *DRD4* allele raised by insensitive mothers displayed more externalizing behaviors than children without the *DRD4* 7-repeat (irrespective of maternal sensitivity), whereas children with the 7-repeat allele raised by sensitive mothers showed the lowest levels of externalizing problem behavior

(Bakermans-Kranenburg & van IJzendoorn, 2007). Such results suggest that conceptualizing the 7-repeat *DRD4* allele exclusively in risk-factor terms is misguided, as this variant of the gene seems to heighten susceptibility to a wide variety of environments, with supportive and risky contexts promoting, respectively, positive and negative functioning.

In the time since I last reviewed such differential-susceptibility-related evidence (Belsky & Pluess, 2009), ever more GXE findings pertaining to DRD4 (and other polymorphisms, see below) have appeared consistent with the notion that there are individual differences in developmental plasticity. Consider in this regard recent differential-susceptibility-related evidence showing heightened—or exclusive—susceptibility of individuals carrying the 7-repeat allele when the environmental predictor and developmental outcome were, respectively, (a) maternal positivity and pro-social behavior (Knafo, Israel, & Ebstein, 2011); (b) early nonfamilial childcare and social competence (Belsky & Pluess, 2013b); (c) contextual stress and support and adolescent negative arousal (Beach et al., 2012); (d) childhood adversity and young-adult persistent alcohol dependence (Park, Sher, Todorov, & Heath, 2011); and (e) newborn risk status (i.e., gestational age, birth weight for gestational age, length of stay in NICU) and observed maternal sensitivity (Fortuna et al., 2011). Especially noteworthy, perhaps are the results of a meta-analysis of GXE research involving dopamine-related genes showing that children eight and younger respond to positive and negative developmental experiences and environmental exposures in a manner consistent with differential susceptibility (Bakermans-Kranenburg & van IJzendoorn, 2011).

As in the case of negative emotionality, intervention research also underscores the susceptibility to 7-repeat carriers of the DRD4 gene to benefit disproportionately from supportive environments. Kegel, Bus and van IJzendoorn (2011) tested and found support for the hypothesis that it would be DRD4 7R carriers who would benefit from specially designed computer games promoting phonemic awareness and, thereby, early literacy in their randomized control trial (RCT). Other such RCT results point in the same direction with regard to DRD4-7R, including research on African-American teenagers in which substance use was the outcome examined (Beach, Brody, Lei, & Philibert, 2010; Brody, Chen, & Beach, 2013; Brody, Chen, Beach, et al., 2013).

5-HTTLPR

Perhaps the most studied polymorphism in research on GXE interactions is the serotonin-transporter gene, *5-HTTLPR*. Most research distinguishes those who carry one or two short alleles (s/s, s/l) and those homozygous for the long

allele (l/l). The short allele has generally been associated with reduced expression of the serotonin transporter molecule--which is involved in the reuptake of serotonin from the synaptic cleft—and thus considered to be related to depression, either directly or in the face of adversity. Indeed, the short allele has often been conceptualized as a "depression gene".

Caspi and associates (2003) were the first to show that the *5-HTTLPR* moderates effects of stressful life events during early adulthood on depressive symptoms, as well as on probability of suicide ideation/attempts and of major depression episode at age 26 years. Individuals with two s alleles proved most adversely affected whereas effects on l/l genotypes were weaker or entirely absent. Of special significance, however, is that carriers of the s/s allele scored best on the outcomes just mentioned when stressful life events were absent, though not by very much.

Multiple research groups have attempted to replicate Caspi et al.'s (2003) findings of increased vulnerability to depression in response to stressful life events for individuals with one or more copies of the s allele, with many succeeding (see below), but certainly not all (e.g., Surtees et al., 2006; Risch et al., 2009). The data presented in quite a number of studies indicates, however, that individuals carrying short alleles (s/s, s/l) did not just function most poorly when exposed to many stressors, but best—showing least problems—when encountering few or none (e.g., Wilhelm et al., 2006). Calling explicit attention to such a pattern of results, Taylor and associates (2006) reported that young adults homozygous for short alleles (s/s) manifested greater depressive symptomatology than individuals with other allelic variants when exposed to early adversity (i.e., problematic childrearing history), as well as many recent negative life events, yet the fewest symptoms when they experienced a supportive early environment or recent positive experiences. The same for-better-*and*-for-worse pattern of results concerning depression are evident in Eley et al.'s (2004) research on adolescent girls who were and were not exposed to risky family environments.

The effect of *5-HTTLPR* in moderating environmental influences in a manner consistent with differential susceptibility is not restricted to depression and its symptoms. It also emerges in studies of anxiety (Stein, Schork & Gelernter, 2008) and ADHD, particularly ADHD which persists into adulthood (Retz et al., 2008). In all these cases, emotional abuse in childhood (Stein et al., 2008) or a generally adverse childrearing environment (Retz et al., 2008), it proved to be those individuals carrying short alleles who responded to developmental or concurrent experiences in a for-better-*and*-for-worse manner, depending on the nature of the

experience in question.

Since last reviewing such 5-HTTLPR-related GXE research consistent with differential susceptibility (Belsky & Pluess, 2009), ever more evidence in line with the just-cited work has emerged. Consider in this regard evidence showing for-better-and-for-worse results in the case of those carrying one or more short alleles of 5-HTTLPR when the rearing predictor and child outcome were, respectively, (a) maternal responsiveness and child moral internalization (Kochanska et al., 2011), (b) child maltreatment and children's antisocial behavior (Cicchetti, Rogosch, & Thibodeau, 2012), and (c) supportive parenting and children's positive affect (Hankin et al., 2011). Differential-susceptibility-related findings also emerged (among male African-American adolescents) when (d) perceived racial discrimination was used to predict conduct problems (Brody et al., 2011); (e) when life events were used to predict neuroticism (Pluess, Belsky, Way, & Taylor, 2010) and (f) life satisfaction of young adults (Kuepper et al., 2012); and (g) when retrospectively-reported childhood adversity was used to explain aspects of impulsivity among college students (e.g., pervasive influence of feelings, feelings trigger action) (Carver, Johnson, Joormann, Kim, & Nam, 2011). Especially noteworthy are the results of a recent meta-analysis of GXE findings pertaining to children under 18 years of age showing that short-allele carriers are more susceptible to the effects of both positive and negative developmental experiences and environmental exposures, at least in the case of Caucasians (Van IJzendoorn, Belsky & Bakermans-Kranenburg, 2013).

As was the case with DRD4, there is also evidence from intervention studies documenting differential susceptibility. Consider in this regard Drury and associates (2012) data showing that it was only children growing up in Romanian orphanages who carried 5-HTTLPR short alleles who benefited from being randomly assigned to high-quality foster care—in terms of reductions in the display of indiscriminant friendliness. Eley and associates (2012) also documented intervention benefits restricted to short allele carriers in their study of cognitive behavior therapy for children suffering from severe anxiety, but their design included only treated children (i.e., did not involve a randomly assigned control group).

Polygenetic Plasticity

Most GXE research, like that just considered, has focused on one or another polymorphism—like *DRD4* or *5-HTTLPR*. In recent years, however, work has emerged focusing on multiple polymorphisms and thus reflecting the operation of epistatic (i.e., GXG) interactions (e.g., Beaver, Sak, Vaske, & Nilsson, 2010; Conner, Hellemann, Ritchie, & Noble, 2010), as well as

GXGXE ones. One can distinguish polygenetic GXE research in terms of the basis used for creating multi-gene composites. One strategy involves identifying genes which show main effects and then compositing only these to then test an interaction with some environmental parameter (e.g., Docherty, Kovas, & Plomin, 2011). Another approach is to composite genes for a secondary, follow-up analysis that have been found in a first round of inquiry to generate significant GXE interactions (e.g., Brody, Chen, & Beach, 2013; Sonuga-Barke et al., 2009). When Cicchetti and Rogosch (2012) applied this approach using four different polymorphisms, they found that as the number of sensitivity-to-the-environment alleles increased (i.e., S/S allele of 5HTTLPR, zero copies of CRH1 TAT haplotype, the TT genotype of DRD4-521C/T, and A carrier of OXTR), so did the degree to which maltreated and non-maltreated low-income children differed on a composite measure of resilient functioning—in a for-better-and-for-worse manner.

A third approach which has now been used successfully a number of times to chronicle differential susceptibility involves compositing a set of genes selected on an a-priori basis before evaluating GXE (e.g., Brody, Chen, & Beach, 2013). Consider in this regard evidence indicating that 2-gene composites moderate links (a) between sexual abuse and adolescent depression/anxiety and somatic symptoms (Cicchetti, Rogosch, & Sturge-Apple, 2007), (b) between perceived racial discrimination and risk-related cognitions reflecting a fast vs. slow life-history strategy (Gibbons et al., 2012), (c) between contextual stress/support and aggression in young adulthood (Simons et al., 2011) and (d) between social class and post-partum depression (Mitchell et al., 2011). Of note, too is evidence that a 3-gene composite moderates the relation between a hostile-demoralizing community and family environment and aggression in early adulthood (Simons et al., 2011) and that a 5-gene composite moderates the relation between parenting and adolescent self-control (Belsky & Beaver, 2011).

Given research already reviewed, it is probably not surprising that there is also work examining genetically moderated intervention effects focusing on multi-gene composites rather than singular candidate genes. Consider in this regard the Drury et al.'s (2012) findings showing that even though the genetic polymorphism brain derived neurotrophic factor, *BDNF*, did not—all by itself—operate as a plasticity factor when it came to distinguishing those who did and did not benefit from the aforementioned foster-care intervention implemented with institutionalized children in Romania, the already-noted moderating effect of 5-HTTLPR was amplified if a child carried Met rather than Val alleles of BDNF *along with*

short 5-HTTLPR alleles. In other words, the more plasticity alleles children carried, the more their indiscriminate friendliness declined over time when assigned to foster care and the more it increased if they remained institutionalized. Consider next Brody, Chen and Beach's (2013) confirmed prediction that the more GABAergic and Dopaminergic genes African-American teens carried, the more protected they were from increasing their alcohol use over time when enrolled in a whole-family prevention program. Such results once again call attention to the benefits of moving beyond single polymorphisms when it comes to operationalizing the plasticity phenotype. They also indicate that even if a single gene may not by itself moderate an intervention (or other environmental) effect, it could still play a role in determining the degree to which an individual benefits. These are insights future investigators—and interventionists—should keep in mind when seeking to illuminate "what works for whom?"

Unknowns in the Differential-Susceptibility Equation

The notion of differential susceptibility, derived as it is from evolutionary theorizing, has gained great attention in recent years, including a special section in the journal *Development and Psychopathology* (see Ellis et al., 2011). Although research summarized here suggests that the concept has utility, there are many "unknowns," several of which are highlighted in this concluding section.

Domain General or Domain Specific?

Is it the case that some children, perhaps those who begin life as highly negatively emotional, are more susceptible both to a wide variety of rearing influences and with respect to a wide variety of developmental outcomes—as is presumed in the use of concepts like "fixed" and "plastic" strategists (Belsky, 2005), with the latter being highly malleable and the former hardly at all? Boyce and Ellis (2005) contend that a general psychobiological reactivity makes some children especially vulnerable to stress and thus to general health problems. Or is it the case, as Belsky (2005) wonders and Kochanska, Aksan, and Joy argue (2007), that different children are susceptible to different environmental influences (e.g., nurturance, hostility) and with respect to different outcomes? Pertinent to this idea are findings of Caspi and Moffitt (2006) indicating that different genes differentially moderated the effect of child maltreatment on antisocial behavior (*MAO-A*) and on depression (*5HTT*).

Continuous Versus Discrete Plasticity?

The central argument that children vary in their susceptibility to rearing

influences raises the question of how to conceptualize differential susceptibility: categorically (some children highly plastic and others not so at all) or continuously (some children simply more malleable than others)? It may even be that plasticity is discrete for some environment–outcome relations, with some individuals affected and others not at all (e.g., gender-specific effects), but that plasticity is more continuous for other susceptibility factors (e.g., in the case of the increasing vulnerability to stress of parents with decreasing dopaminergic efficiency; van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008. Certainly the work which composites multiple genotypes implies that there is a "plasticity gradient", with some children higher and some lower in plasticity (Belsky & Pluess, 2009).

Mechanisms

Susceptibility factors are the moderators of the relation between the environment and developmental outcome, but they do not elucidate the mechanism of differential influence. Several (non-mutually exclusive) explanations have been advanced for the heightened susceptibility of negatively emotional infants. Suomi (1997) posits that the timidity of "uptight" infants affords them extensive opportunity to learn by watching, a view perhaps consistent with Bakermans-Kranenburg and van IJzendoorn's (2007) aforementioned findings pertaining to *DRD4*, given the link between the dopamine system and attention. Kochanska et al., (2007) contend that the ease with which anxiety is induced in fearful children makes them highly responsive to parental demands. And Belsky (2005) speculates that negativity actually reflects a highly sensitive nervous system on which experience registers powerfully—negatively when not regulated by the caregiver but positively when coregulation occurs—a point of view somewhat related to Boyce and Ellis' (2005) proposal that susceptibility may reflect prenatally programmed hyper-reactivity to stress.

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